Genetic Modification of Airway Progenitors Following Lentiviral Gene Delivery to the Amniotic Fluid of Murine Fetuses.

Journal: Am J Respir Cell Mol Biol

Publication Year: 2010

Authors: S Mishra, X Wang, N Smiley, P Xia, C M Hong, D Senadheera, K C Bui, C Lutzko

PubMed link: 20581098

Funding Grants: Training Grant 1

Public Summary:
Lentiviral vectors with the firefly luciferase or EGFP transgenes were delivered to the amniotic fluid of murine fetuses at E14.5 or E16.5. Whole body imaging of luciferase recipients after birth demonstrated transgene expression in the peritoneal and thoracic regions. Organ imaging showed luciferase expression in lung, skin, stomach and/or intestine. Histological immunofluorescence analysis of EGFP recipients demonstrated that small clusters (< 3 cells) of EGFP positive epithelial cells were present in the large and small airways of recipients at up to seven months (N=11). There was no difference in the frequency of transgene expression in mice injected at E14.5 or E16.5 in respiratory or non-respiratory organs. Analysis of the bronchioalveolar duct junctions on tissue sections of recipient mice identified multiple EGFP positive epithelial cells. Cells co-expressing EGFP, CC10, and SPC were also found in lungs, consistent with the transduction of bronchioalveolar stem cells. Next, naphthalene lung injury in both luciferase and EGFP recipients was performed to determine whether transduced cells could contribute to tissue repair. In luciferase recipients, the whole body luciferase signal increased 2 to 20-fold at two weeks after naphthalene treatment. Remarkably, immunohistological analysis of the lungs of EGFP recipients following lung injury repair demonstrated repopulation of airways with long stretches of EGFP positive epithelial cells (N=4). Collectively, this data demonstrates that lentiviral gene delivery to the amniotic fluid of murine fetuses genetically modifies long-lived epithelial progenitors capable of contributing to lung injury repair.

Scientific Abstract:
Lentiviral vectors with the firefly luciferase or EGFP transgenes were delivered to the amniotic fluid of murine fetuses at E14.5 or E16.5. Whole body imaging of luciferase recipients after birth demonstrated transgene expression in the peritoneal and thoracic regions. Organ imaging showed luciferase expression in lung, skin, stomach and/or intestine. Histological immunofluorescence analysis of EGFP recipients demonstrated that small clusters (< 3 cells) of EGFP positive epithelial cells were present in the large and small airways of recipients at up to seven months (N=11). There was no difference in the frequency of transgene expression in mice injected at E14.5 or E16.5 in respiratory or non-respiratory organs. Analysis of the bronchioalveolar duct junctions on tissue sections of recipient mice identified multiple EGFP positive epithelial cells. Cells co-expressing EGFP, CC10, and SPC were also found in lungs, consistent with the transduction of bronchioalveolar stem cells. Next, naphthalene lung injury in both luciferase and EGFP recipients was performed to determine whether transduced cells could contribute to tissue repair. In luciferase recipients, the whole body luciferase signal increased 2 to 20-fold at two weeks after naphthalene treatment. Remarkably, immunohistological analysis of the lungs of EGFP recipients following lung injury repair demonstrated repopulation of airways with long stretches of EGFP positive epithelial cells (N=4). Collectively, this data demonstrates that lentiviral gene delivery to the amniotic fluid of murine fetuses genetically modifies long-lived epithelial progenitors capable of contributing to lung injury repair.